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"TRANSITION METAL DONOR-PEPTIDE-ACCEPTOR COMPLEXES: FROM INTRAMOLECULAR ELECTRON TRANSFER REACTIONS TO THE STUDY OF REACTIVE INTERMEDIATES"

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FINAL REPORT

DISCLAIMER

LONG RANGE ELECTRON TRANSFER IN POLYPROLINE PEPTIDES:

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I. Executive Summary

The trans-polyproline **(PII)** oligomers (Figure 1) are unusually rigid peptide structures which have been extensively studied by our group for peptide mediated intramolecular electron transfer (ET) at long distances.[1-4] We have prviously studied ET across a series of metal ion donor (**D**) acceptor (**A**) oligoproline peptides with different distances, driving forces and reorganizational energies. The majority of these experiments involve generating the ET intermediate using pulse radiolysis methods, although more recently photochemical methods are also used.

Results of these studies showed that ET across peptides can vary by more than twelve orders of magnitude. Using ruthenium bipyridine donors, ET reaction rate constants across several proline residues (n = 4 - 9) occurred in the millisecond (ms) to μs timescale, thus limiting the proline peptide conformational motions to only minor changes (far smaller than the large changes that occur on the ms to sec timescale, such as trans to cis proline isomerization).[1]

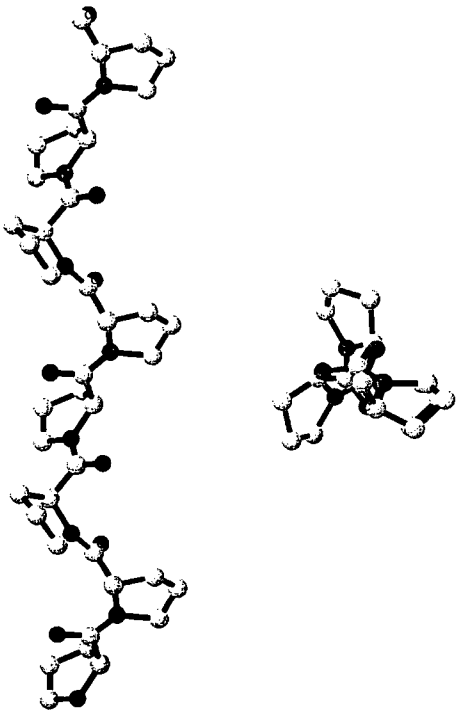


Figure 1. Three dimensional stucture of Poly-L-Proline II viewed along the xy and z axis.

The present report describes our large data base of experimental results for **D**-peptide-**A** complexes in terms of a model where the involvement of both superexchange and hopping (hole and electron) mechanisms account for the long range ET rate constants observed. Our data shows that the change from superexchange to hopping mechanisms occurs at different distances depending on the type of **D** and **A** and

their interactions with the peptides. Our model is also consistent with generalized models for superexchange and hopping which have been put forward by a number of theoretical theoretical groups to account for long range ET phenomena. [5-14]

Relationship of this Project to DOE Sponsored Programs

Peptide and amide matrices are constituents of natural and industrial polymers (e.g polyamides and nylons). Peptide structural motifs provide versatile matrices that can be used to study the factors that control long range ET in a systematic manner. Such an understanding will have important implications in designing molecules that can effect efficient photochemical charge separation and storage.[15] For longer term applications, using peptide bridging groups to hold components of reactions such as light absorbers and catalytic metal binding sites together could offer many advantages over other matrices because of the predictable synthetic procedures and the self assembly properties of certain classes of peptides. Our studies show that peptide bridging groups can provide large spatial separation between light absorbing chromophores while maintaining adequate electronic communication between them. Nanostructured materials with light absorbing chromophores can be controllably self-assembled from the molecules studied in this proposal.

II. Project Accomplishments and summary

A. Long Range Electron Transfer in Peptides: Theory and Experiments

Rates of ET between two sites for a non-adiabatic electron transfer (k_{et}) can be described as the product of an electronic and a nuclear factor using the Marcus equation [10,16-18]

$$k_{et} = 4\pi^2/h\,[H_{DA}(r)]^2\,(4\pi\lambda kT)^{-1/2}\exp[-(\Delta G_i^{\circ} + \lambda)^2 / 4\lambda kT] \qquad (1)$$

with the driving force ($^{-}G_{¡}$), the reorganization energy (λ), and the electronic coupling matrix element (H_{DA}). The electronic coupling matrix element defines the extent of the overlap between the reactant and product wave functions during the ET process (($H_{DA}(r)$) and can therefore control the magnitude of the rate constant at long distances. The rate constant, k_{et} is expected to decrease exponentially with the increase in **D-A** separation according to equation 2,

$$H_{DA}(r) = H_{DA¡} \exp [—\beta(r - r_{o})/2] \qquad (2)$$

where $H_{DA¡}$ is the electronic coupling at van der Waals contact, r is the **D-A** separation distance and r_o is the sum of the van der Waal radii of the **D** and the **A**, β is the distance attenuation factor.

Studies on the electron mediation properties of polypeptides have used a number of different **D**-peptide-**A** complexes in the last decade [11,19-48]. The common theme in these studies is the quest for understanding the distance dependence of ET across polypeptides and the distinction between different electronic interactions occurring through covalent and/or non-covalent bonding.

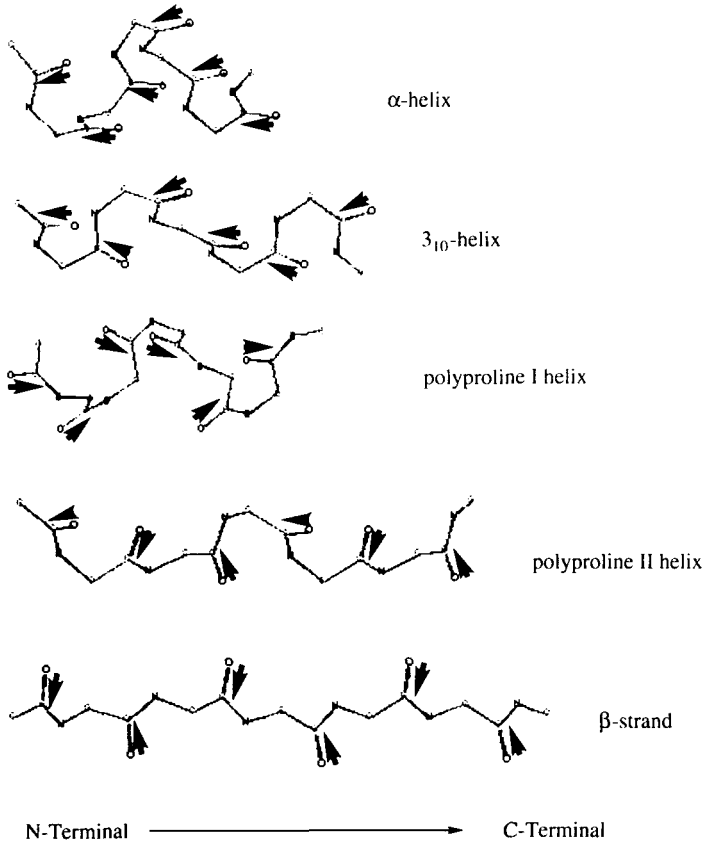


Figure 2. Orientation of dipoles in a series of pentapeptides with different secondary structure.

A special feature of peptides which distinguishes

them from hydrocarbon polymers is that ET across peptides can depend on the direction of peptide dipoles between the **D** and **A**, as well as, on the reorganization energy, driving force, and distance. In dipole generating structures ET rates occurring in the direction of the peptide dipole will be greater than those occurring against the direction of the dipole, while in structures with no orientational dipole, the direction of ET will have no effect on rates (Figure 2). An example of this dipole dependence predicted by theory has been recently shown experimentally for an α-helix where large molecular dipoles across the peptide are present. In the oligoproline **D**-peptide-**A** complexes no such large dipoles are present and therefore ET rates are not expected to be dependent on the direction of the transfer. [38-40]

In the absorption spectra of oligoprolines in aqueous solution (Figure 3), the absorption bands assigned to different n to π* and π to π* transitions of the peptide backbone transitions shift to lower energies as the oligomer size increases.[49] Compared to other peptides, this UV is indicative of the organized rigid triple helical structure of oligoprolines and the λ_{max} in these absorption spectra is a guide to the energetics for ET through these bridging ligands. The PI and PII are the high molecular weight oligoprolines. These oligoprolines also have characteristic CD spectra in the UV region which will be shown later (Figure 8).

In our studies of $[(bpy)_2Ru^{II}cmbpy\text{-}(Pro)_n\text{-}apyRu^{III}(NH_3)_5]$ (Figure 4, red triangles) (where cmbpy = carboxy 4-methyl 2,2 bipyridine, apy = 4-aminopyridine) an attenuation factor $\beta \sim 1.0 - 1.4$ $^{-1}$ was found for the shorter peptides n = 0 — 3, while a small attenuation factor, $\beta = 0.2 - 0.3$, was observed for the longer oligoprolines (n = 4 — 9). [1-3] This small attenuation factor βwas also observed in the studies of similar oligoproline peptides with different donors and acceptors by Klapper and Faraggi[24], Bobrowski[27], Maruyama.[36]

In order to compare different rates of ET which occur with different ˜G_i and λ , an activationless rate constant, k_{max}, can be defined as

$$\ln k_{et}^{max} = \ln k_{et} + (\lambda + \Delta G°)^2/4\lambda RT \quad (3)$$

$$k_{max} = k_{max} \exp[-\beta(r - r_o)] \quad (4)$$

where the maximum ET rate ($k°_{max} \sim 10^{12} - 10^{13}\ s^{-1}$) is expected at r_o, the van der Waal radii distance between the **D** and the **A**). With Eq 3 and 4, rate constants for reactions studied at different driving forces, reorganization energies, and distances can now be compared.[16] Using this k_{max} method, $\beta \sim 0.7 - 1.4$ [-1] values have been reported for many **D**-peptide-**A** complexes (including protein bridges which are more difficult to define).[50] The significance of the two attenuation values β and β and their mechanistic implications will now be discussed.

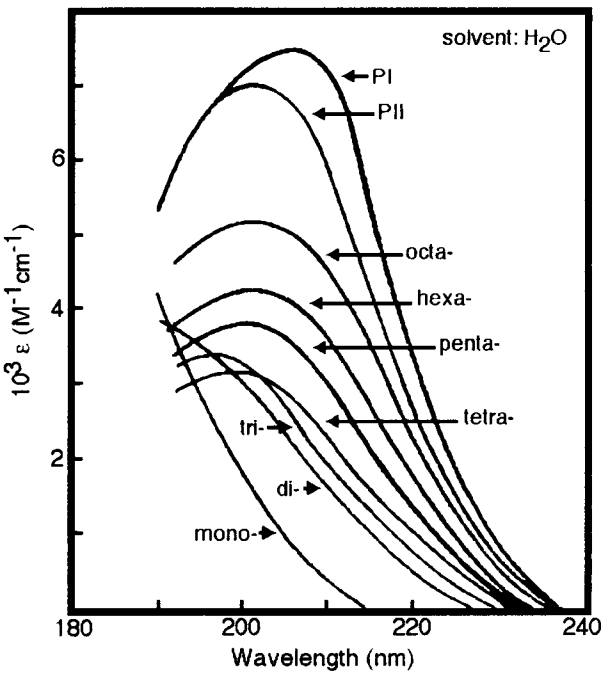


Figure 3. UV spectra of oligoprolines in aqueous solution showing a shift to lower energy as the number of proline residue increases in the polymer.

Until recently, the superexchange mechanism (where electron or hole transfer occurs from the initial state across the bridge to the final state in a single step) was the dominant mechanism used to interpret long range ET in hydrocarbon, peptide and protein bridged long range ET reactions.[51] However, the rapid rates which occur at long distances could not be accounted for by superexchange mechanisms. The recent studies of long range ET in DNA duplexes necessitated the use of alternative models to explain the observations of ET at long distances.[51,52] The rates at long distances in DNA duplexes were best accounted for by a hole hopping mechanism, where multistep electron transport reactions occur between the donor, the bridge, and the acceptor.

In proteins covalently modified with redox reagents, the distance dependence of the ET rate for the superexchange mechanism is defined by the attenuation factor β, where β ~0.7 — 1.4 $^{-1}$. [53-55] In our investigations of long range ET across oligoproline peptides an additional smaller attenuation factor β ~0.2 was observed at long distances. [1,56] We now assign this small attenuation factor at long distances to a hopping mechanism. Depending on the energetics of the **D** and **A** this could be a hole or an electron hopping mechanism. The hopping mechanism is expected to depend significantly on the coupling between the donor and the peptide bridge.[57] If the bridge — bridge and the bridge acceptor ET reactions are fast, then the rate limiting step will be the coupling between the donor and the bridge. In addition to measurement of the ET rate constants other experiments, such as temperature dependence of rates, kinetics in viscous and rigid media, and the determination of intervalence transitions between the donor and the acceptor are necessary to distinguish between superexchange and hopping. The long range of distances covered in our experiments with peptide bridging ligands (~10 — 40), using a variety of transition metal donors and acceptors led to the observation of different distance of the two attenuation factors β and β for ET rates. This is taken as an indication of a smooth transition between the superexchange and the hopping mechanisms. Such a transition has been predicted many years ago by theoretical models,[6,7] [8,9] but no clear experimental results spanning long distances were available to test these models.

B. Summary of our Intramolecular Electron Transfer Studies Across Oligoproline Bridges

i. Metal to Metal Distances across Oligoproline Peptide Bridges

Proline is a unique amino acid among the 20 naturally occurring amino acids. It has a secondary amine terminal and is also conformationally constrained by cyclization. These characteristics result in unusually rigid structures and slow conformational changes

for oligoproline peptides compared to other polyamino acids.[1] The **D-A** distances across the oligoprolines were estimated from X-ray[58,59] and NMR solution structures (using data from crystal and fiber structures of Pro oligomers and the solution NMR structure of $[(NH_3)_5Co(Pro)_5]$). [60] For the **PII** structures all these techniques showed that every additional Pro residue increases the through space **D-A** distance by 3.12 . Similar distances for oligoproline residues were also estimated from the classic experiments of Stryer, et. al. [61] on energy transfer across $(Pro)_n$ (n = 5 — 12) and more recent work of Tamiaki, et. al.[36] on energy and electron transfer between Zn and Fe porphyrins separated by $(Pro)_n$ (n = 4 — 8). The interpretation of all our ET rates for n = 0-9prolines relies on the **D-A** distance estimates obtained in these prior studies.

ii. Determination of Maximum ET Rates and Attenuation Factors β and β' in Metal Ion D-A Complexes

Using these metal to metal distances a plot of k_{max} vs distance for Pro molecules bridged by a variety of transition metal complexes with different driving forces and reorganization energies (Table 1, Figure 4) shows that the measured rates across Pro bridges vary by more than 12 orders of magnitude.[1] In spite of the imprecise corrections to calculate k_{max}, the ET rates (Figure 4, Table 1) clearly fall into two separate regimes, a

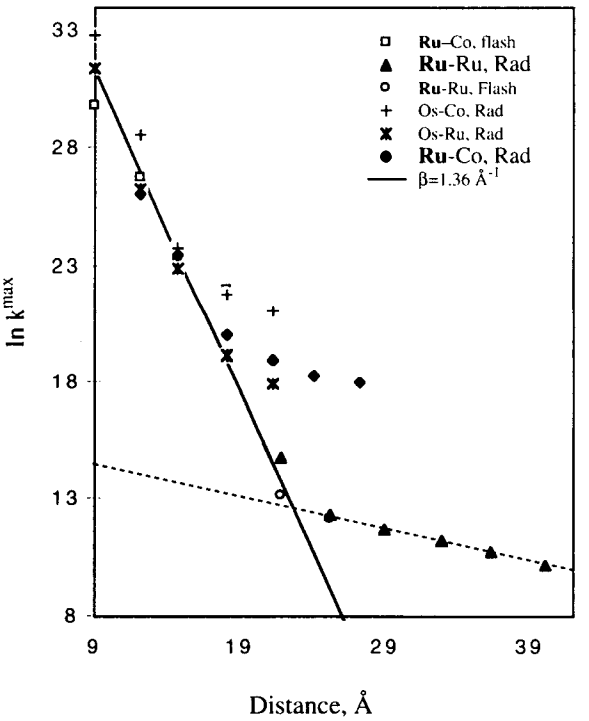


Figure 4. Maximum ET rates across oligoproline peptides with different metal ion donors and acceptors. In **Ru**-Ru, Rad and **Ru**-Co, Rad series the donor is the Ru'I'-bpy generated by pulse radiolysis.

very fast ET regime, followed by a slow ET regime. Our current interpretation is that the rapid rates of ET belong to the superexchange and the rates with the small attenuation factor, $\beta \sim 0.2$ $^{-1}$, belong to the hopping mechanism.

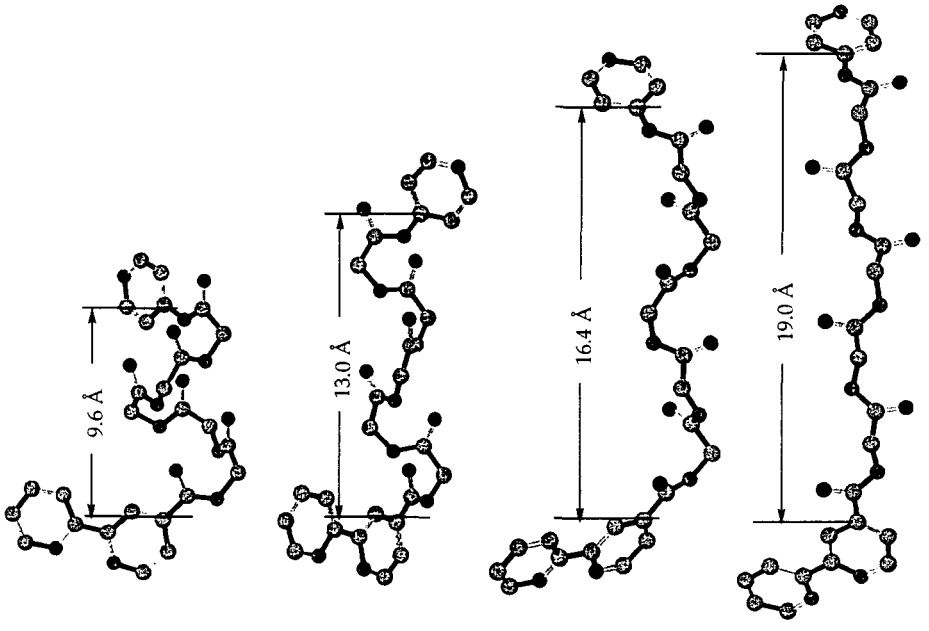
Table 1. Maximum ET Rates for **D**-(pro)$_n$-**A** complexes (n = 0 - 9) Data from ref. 1.

n	d (Å)[a]	ln k_{et}	λ_{reorg} (kcal/mol)[b]	ln $k_{et}^{max.}$ [c]
	$[(bpy)_2Ru^{II}mcbpy]^{\bullet}$-(pro)$_n$-$Co^{III}(NH_3)_5$		-ΔG° = 1.32 V	λ_{in} =71.3 kcal/mol
1	12.2	20.0	14.8	21.5
2	14.8	16.6	15.6	20.0
3	18.1	12.3	16.0	18.9
4	21.3	10.8	16.4	17.4
5	24.1	8.9	16.7	16.2
6	27.3	9.2	16.9	14.8
	$[(bpy)_2Ru^{II}mcbpy]^{*}$-(pro)$_n$-$Co^{III}(NH_3)_5$		-ΔG° = 1.10 V	λ_{in} =71.3 kcal/mol
0	9.0	23.3	13.5	29.4
1	12.2	18.4	14.8	26.1
2	14.8	13.9	15.5	23.4
3	18.1	11.9	16.0	22.0
	$[(bpy)_2Ru^{II}mcbpy]^{\bullet}$-(pro)$_n$-ap$Ru^{III}(NH_3)_5$		-ΔG° = 1.20 V	λ_{in} =3.1 kcal/mol
4	21.9	14.7	7.3	17.3
5	25.2	12.3	7.5	15.7
6	29.0	11.6	7.8	14.0
7	33.0	11.1	8.0	12.1
8	36.3	10.5	8.1	10.6
9	40.1	9.9	8.2	8.8
	$[(bpy)_2Ru^{II}mcbpy]^{*}$-(pro)$_n$-ap$Ru^{III}(NH_3)_5$		-ΔG° = 1.1 V	λ_{in} =3.1 kcal/mol
4	20.67	13.5	7.1	13.5
5	21.9	13.2	7.3	13.3
	$(NH_3)_5Os^{II}$-*i*-nic-(pro)$_n$-$Co^{III}(NH_3)_5$		-ΔG° = 0.40 V	λ_{in} =74.2 kcal/mol
0	9.0	12.2	16.3	34.1
1	12.2	5.6	17.6	29.1
2	14.8	-0.3	18.3	25.1
3	18.1	-3.2	18.8	19.9
4	21.3	-4.6	19.2	14.9
	$(NH_3)_5Os^{II}$-*i*-nic-(pro)$_n$-$Ru^{III}(NH_3)_5$		-ΔG° = 0.25 V	λ_{in} =6.0 kcal/mol
0	9.0	22.3	7.9	31.4
1	12.2	14.9	9.2	26.3
2	14.8	10.5	9.9	22.9
3	18.1	5.8	10.4	19.1
4	21.3	3.9	10.8	17.9

i. edge-to-edge distance based on the β-*trans*-polyproline powder diffraction data

ii. $= \lambda_{out} + \lambda_{in}$. $\lambda_{out} = 45.6 \times (1/2a_1 + 1/2a_2 - 1/d)$ kcal/mol in water, where a[$(M(bpy)_3$] = 7.0Å, a[$M(NH_3)_5$] = 3.5Å and a[ap$M(NH_3)_5$] = 4.0Å. λ_{in} *from ref* . *In* $k^{max} = \ln k^{obs} + (\tilde{}G^{o} + \lambda)^2/4\lambda RT)$, *since* $k^{obs} = k^{max} \exp(-(\tilde{}G^{o} + \lambda)^2/4\lambda RT)$.

Energetics and Electronic Coupling Across Peptide Bridging Units of Different Secondary Structure



	α-helix	3_{10}-helix	pro II-helix	β-sheet
μ_{ab}, Å	4.0	13.0	15.4	20.5
H_{ab}, cm^{-1}	84	12	400	0.1
$k_{et}^{x} / k_{et}^{pro}$	4×10^{-2}	8×10^{-4}	1.0	6×10^{-8}

Figure 5. Donor acceptor distances for (bpy)—(gly)5—ap in different secondary structure conformations. The dipole moment of the peptides, their calculated H_{DA} values, and relative rates (k_{et}peptide/ k_{et}pro) are shown.

For peptides with different secondary structures ZINDO calculations (carried out in collaboration with Dr. Marshall Newton) have shown that for charge separation in **D**-Peptide-**A** complexes, the **PII** structure has a smaller distance attenuation factor than that for α-helices, 3_{10}-helices, and β-strands. An example of this is shown for n = 5 amino acids in different secondary structures terminated by py and bpy at the C and N terminals (Figure 5). Based on these calculations, the dependence of H_{DA} on distance can be

calculated for the different secondary structures with one to six peptide units separating the bpy from the apy terminals (Figure 6).[62] One of the interesting results of these calculations is the lower attenuation factor observed for the oligoproline conformation (Figure 6). In addition to these neutral molecules, the coupling between two adjacent dipeptides was found to be sensitive to the secondary structure of the dipeptide, while in similar dipeptide radical *anions*, the coupling was not sensitive to the secondary structure (Figure 7). While H_{DA} in the radical *anions* did not change appreciably, the differences in the H_{DA} for the radical *cations* in a β strand, an α helix, and a **PII** structure is more than a factor of 30. If the dipeptide radical *cation* corresponds to the hole, and the radical *anion* corresponds to the electron superexchange mechanisms, then the secondary structure sensitive ET rates are expected to occur by the hole transfer mechanism (via filled peptide π orbitals) rather than by the electron transfer mechanism (via peptide π* orbitals). This important difference between the radical cation and anion behavior will be used later to interpret the recent experimental results obtained on long range ET in peptides.

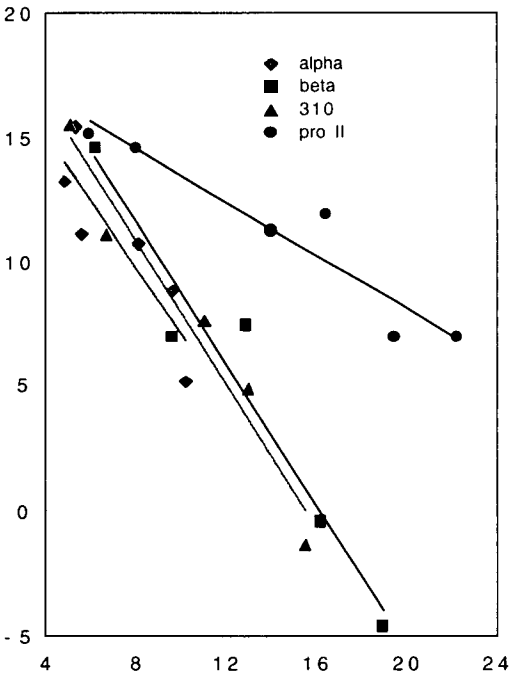


Figure 6. Distance Dependence of H_{AB} for Different Peptide Secondary Structures Determined from the Energetics and Electronic Coupling Using ZINDO Calculations.

Sec. Structure	H_{DA} Anionic Peptide	H_{DA} Cationic Peptide
α-helix	777	1324
β-strand	853	50
polypro II	769	870
3_{10}-helix	185	391

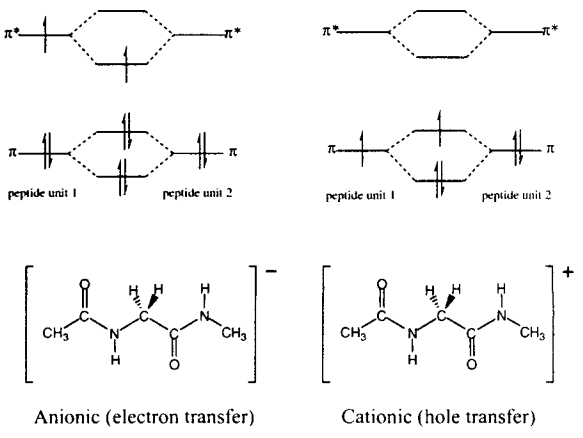


Figure 7. The value of H_{DA} (cm-1) for LUMO's and HOMO's of a Dipeptide Radical *Cation* and an *Anion*.

iv. Influence of the Donor Peptide Interactions on Long Range ET Rates in Rigid and Flexible Peptides

Experiments on **D**-Peptide-**A** complexes, where the secondary structure was altered by introducing a number of different non-*l*-proline residues to perturb the rigid proline secondary structure were carried out (Figure 8). Such a systematic variation in the bridging peptide would test the importance of the **PII** structure in these ET reactions. The amino acids glycine, sarcosine, β-alanine and *d*-proline were used to replace one or two *l*-prolines in a series of hexapeptides.[63] This hexapeptide length $(pro)_6$ was chosen because it separates the **D** from the **A** by a large distance (~30) and forms a stable **PII** secondary structure where two helical peptide turns separate the **D** from the **A**. Surprisingly, for eight different peptides no correlation between the peptide secondary structure (as seen by the CD of the peptides) with their ET rates was observed. The same rate constant, $k_{et} = 1.1 - 0.2 \times 10^5$ sec^{-1}, was observed for all eight peptides (Figure 8). These results, though initially disappointing (because of the effort to assemble the series), do in fact agree with the ZINDO calculations (Figure 7) for peptide radical *anions* where adjacent peptide interactions are not sensitive to secondary structure. The bpy radical anion donor in $Ru(bpy)_3^{2+}$ which has a reduction potential, ~ -1.5 V vs SCE (Figure 7) is estimated to lie ~ 0.4 V below the peptide radical *anion* states. Such an estimate is obtained from our data for the Ru-peptide-Ru series (Table 1). [The ˜G ° for ET from the donor bpy to the peptide was calculated using the intercept of the k_{max} vs distance plot (Figure 4, red triangles) and assuming the reorganization energy of the donor to peptide step is the same as the overall reaction reorganization energy].

If one uses a multistep hopping mechanism to describe these reactions, three separate steps must be considered: the **D** to bridge, the bridge to bridge, and the bridge to **A** reactions. The first of these three reactions, the **D** to bridge transfer, would be rate limiting. This is because the second step, adjacent peptide-peptide interactions are thermo-neutral and rapid with a large electronic coupling matrix element between them

(H_{AD} ~ 800 cm^{-1} for radical anions) (Figure 7).[62] The third reaction, peptide to **A**, should be very rapid, since it occurs with a very large driving force, >1 V. If this analysis holds, then any changes in the donor-peptide interactions should result in large changes in overall ET rates. In the next series of experiments we will show our first attempts to alter the donor to peptide interactions with minimal effects on the driving force and reorganization energy for these long range ET reactions.

$$Ru^{II}\dot{-}cmbpy(AA)_6apyRu^{III} \xrightarrow{k_{et}} Ru^{II}cmbpy(AA)_6apyRu^{II}$$

Oligoproline helical reference:

$[(bpy)_2Ru^{II}cmbpy\text{-}Pro_6\text{-}apyRu^{III}(NH_3)_5]Cl_5$ (P6)

Partially helical complexes:

$[(bpy)_2Ru^{II}cmbpy\text{-}Pro_3\text{-}Gly\text{-}Pro_2\text{-}apyRu^{III}(NH_3)_5]Cl_5$(G)

$[(bpy)_2Ru^{II}cmbpy\text{-}Pro_2\text{-}Gly_2\text{-}Pro_2\text{-}apyRu^{III}(NH_3)_5]Cl_5$(G2)

$[(bpy)_2Ru^{II}cmbpy\text{-}Pro_3\text{-}\beta\text{-}Ala\text{-}Pro_2\text{-}apyRu^{III}(NH_3)_5]Cl_5$(A) (One more CH_2)

N- alkyl aminoacids and other Imide bond mimics

$[(bpy)_2Ru^{II}cmbpy\text{-}Pro_3\text{-}Sar\text{-}Pro_2\text{-}apyRu^{III}(NH_3)_5]Cl_5$(S1)

$[(bpy)_2Ru^{II}cmbpy\text{-}Pro_2\text{-}Sar_2\text{-}Pro_2\text{-}apyRu^{III}(NH_3)_5]Cl_5$(S2)

$[(bpy)_2Ru^{II}cmbpy\text{-}Pro_3\text{-}d\text{-}pro\text{-}Pro_2\text{-}apyRu^{III}(NH_3)_5]Cl_5$(D)

Flexible random coil reference:

$[(bpy)_2Ru^{II}cmbpy\text{-}Gly_6\text{-}apyRu^{III}(NH_3)_5]Cl_5$(G6)

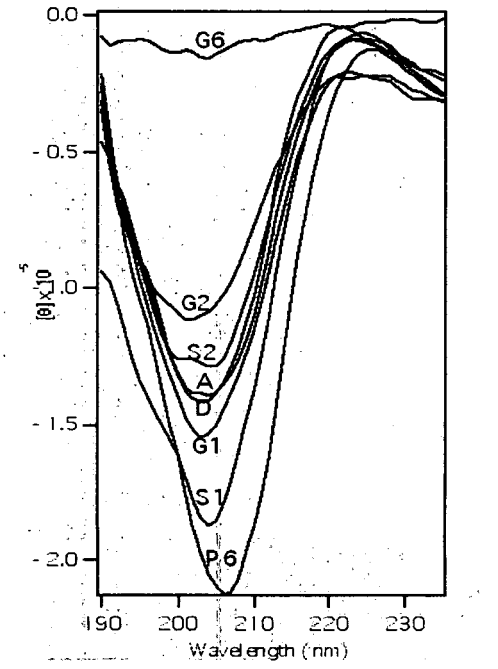


Figure 8. CD Spectra of the Peptide Sequences showing the different amounts of **PII** structure in the different peptides.

v. Decreasing the Donor-Peptide Interaction in a Series of Peptide Bridged Complexes by Introducing (4,4 diCF$_3$bpy)$_2$Ru^{II} to the Donor Site

To decrease the **D**-peptide interaction, a CF$_3$bpy[64,65] (where CF$_3$bpy = 4,4'diCF$_3$bpy) was used to replace bpy at the donor sitedonor site. For a series of CF$_3$bpy-**D**-peptide-**A** complexes, we selected three hexapeptides, Pro$_6$, Pro$_2$Gly$_2$Pro$_2$, and Gly$_6$, as prototypes representing rigid, intermediate rigidity, and flexible bridges. In the CF$_3$bpy-**D**-peptide-**A** complexes the intramolecular ET is expected to proceed from the more electron withdrawing CF$_3$bpy ligand to the bpy carrying the peptide bridge and then to the acceptor. In contrast, in the bpy-**D**-peptide-**A** with the bpy directly bound to the peptide, the first reduction occurs on the ligand covalently bound to the peptide bridge. Such a change is expected to affect the **D** to bridging peptide interactions significantly. Although ˜G° for the ET reaction in the CF$_3$bpy series decreases from that in the bpy series, it is still large enough so that the ET rate is close to k_{max} for this series.

The ET kinetics for these three complexes showed that for the Pro$_2$Gly$_2$Pro$_2$, and Gly$_6$ bridges, intramolecular ET rates were slow and could not be observed (Table 2). An upper limit, $k < 1 \times 10^3$ s^{-1}, is estimated for both bridges. [63] The slow rate constant for the very flexible Gly$_6$ bridge (even at 2 μmolar concentrations) would not have been predicted (because of the flexibility of Gly$_6$ to possibly bring the **D** and **A** to close proximity). However, for the Pro$_6$ bridge a large intramolecular rate constant, 2.4×10^4 s^{-1} was observed, indicative of the effectiveness of

Complex μM	Intra. $10^4 k_{et}$ (s^{-1})	Inter. $10^9 k_{et}$ ($M^{-1}s^{-1}$)
RuPro$_6$-apyRu	3.7–0.3	2.2–0.2
RuP$_2$G$_2$P$_2$-apyRu	< 0.3	2.4–0.2
RuG$_6$-apyRu	<0.1	2.4–0.2

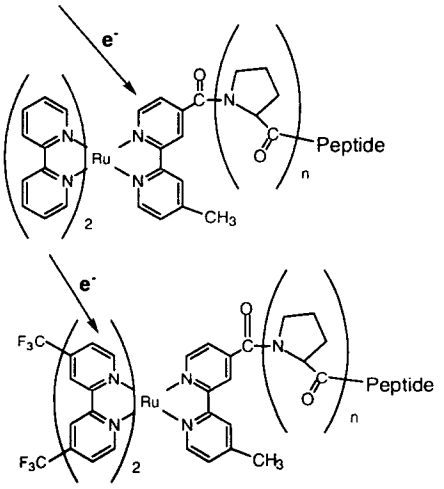
Table 2. Intramolecular and intermolecular ET rate constants for the [(CF$_3$bpy)$_2$Ru^{II}cmbpy-hexapeptide-apyRu^{III}(NH$_3$)$_5$]Cl$_5$ complexes.

the oligoproline bridge as an ET mediator. [63]

The ET results for the three hexapeptide complexes can be understood by assuming a decreased interaction between the donor bpy and the bridge because the $(CF_3bpy)_2Ru^{II}$ donor is easier to reduce than bpy and cmbpyRu (Figure 9).[65] This decreases the interaction between the donor and the bridge and makes the electron superexchange mechanism less efficient. The hole superexchange, where the peptide π orbitals (not the π^*) are involved seems to be the preferred mechanism when CF_3bpy is part of the electron donor. With hole superexchange, the Pro_6 rate constant is expected to be faster than the $Pro_2Gly_2Pro_2$, and Gly_6 rates, because of its more mediating secondary structure. These results are consistent with the ZINDO calculations (Figures 6 and 7).[62] New experiments shown in the next section will be carried out to further substantiate this hypothesis.

Studying Superexchange and Hopping Electron and Hole Mechanisms using Oligoprolines

Our completed work above shows a coherent picture of the ET rates versus distance in the **D**-peptide-**A** complexes studied, which is in agreement with the electronic structure calculations (ZINDO) carried out for the organic bridging groups without the metal ions.[62] The rate constants for the different **D**-peptide-**A** series are accounted for by using electron and hole superexchange and hopping mechanisms. This model applies to all our work, and to other investigations of distance



E^0 of bipyridine ligands
-1.48 V
-1.57 V
-1.80 V
-1.08 V
-1.27 V
-1.44 V

Rigid helical peptide:
$[(DTFM\text{-}bpy)_2Ru^{II}cmbpy\text{-}Pro_6\text{-}apyRu^{III}(NH_3)_5]Cl_5$
Partially helical peptide:
$[(DTFM\text{-}bpy)_2Ru^{II}cmbpy\text{-}Pro_2Gly_2Pro_2\text{-}apyRu^{III}(NH_3)_5]Cl_5$
Flexible peptide:
$[(DTFM\text{-}bpy)_2Ru^{II}cmbpy\text{-}Gly_6\text{-}apyRu^{III}(NH_3)_5]Cl_5$

Figure 9. Reduction potentials and site of first reduction of bpy and CF_3bpy Ruthenium complexes and their effects on donor to peptide coupling interactions.

dependence of ET rates across polypeptides.[24] Furthermore, the electronic structure calculations (ZINDO) also provide an extremely useful guide for future experiments.

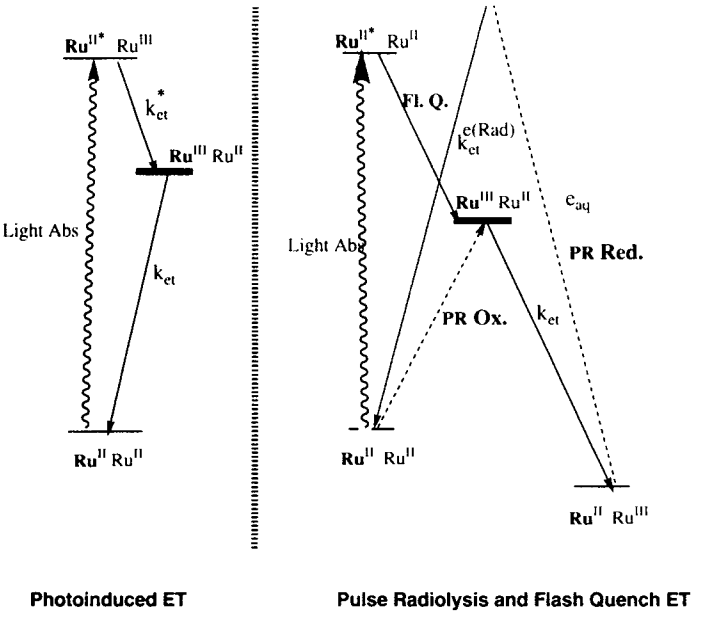


Figure 10. The different ET reactions studied by photoinduced and pulse radiolysis techniques.

A schematic of the different ET reactions determined using both photoinduced and pulse radiolysis techniques in a Ru-peptide-Ru series is shown in Figure 10. The ET reaction across peptides with the reaction intermediate formed using the e_{aq} generated by pulse radiolysis is shown in blue. The photoinduced rate constant k_{et} (in red) refers to the common reaction which can be studied by both pulse radiolysis and flash photolysis.

IV. **References**

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V. Background/Experience of the Principal Investigator

A. Brief Vita

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Education

American University of Beirut, Lebanon, B.S., Chemistry, 1967
American University of Beirut, Lebanon, M.S., Physical Chemistry, 1969
Stanford University, California, Ph.D., Inorganic Chemistry, 1974
University of California, Berkeley, CA, Postdoctoral Fellow, 1974-1975

Appointments

Department of Chemistry, Rutgers The State University of New Jersey
- Professor II, 1989-present
- Professor, 1984-1988
- Associate Professor, 1980-1984
- Assistant Professor, 1975-1980

University and External Professional Activities

Faculty Research Collaborator, Brookhaven National Labs, 1982 - present
Member of NIH Biomedical Science Study Section, 1990-1994
Adjunct Faculty, The Rockefeller University, New York, NY.
(Research with Professor R.B. Merrifield, 1977 - 1978)
Member Rutgers University Committee of Standards and Priorities in Academic Development (CSPAD) 1989 - 1996
Member Rutgers University Research Council 1984-94
Member Rutgers University Busch and BSRG Research Panel 1981-90
Chair Rutgers University Busch and BSRG Research Panel 1985-86
Member, Biochemistry Graduate Program, Rutgers 1978-present
Member, American Chemical Society
Member, American Association for the Advancement of Science

Honors and Awards

NIH Career Development Award, 1980-1985
Camille & Henry Dreyfus Teacher-Scholar Award, 1982-1986
Johnson and Johnson Discovery Research Fellow 1988-1990
Board of Trustees Award for Excellence in Research, Rutgers University, 5/1989
Rutgers University Faculty Fellowship, January 1979 - May 1979

B. Publications (1994-1999)

Electron Transfer from the Heme of Cytochrome c to two Equidistant Redox-modified Sites, Histidine 33 and Methionine 65 - the Importance of Electronic Effects and Peptide Networks. Moreira I.; Sun J.; Cho, M-oK. Wishart .J.F.; Isied S..S. *J.Am. Chem. Soc.* **1994**, 116 :8396-8397.

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"cis-Bisbipyridine Ruthenium Imidazole Derivatives: A Spectroscopic, Kinetic, and Structural Study" Reddy, K. B.; Cho, M.-o. P.; Wishart, J. F.; Emge, T. J.; Isied, S. S. *Inorg. Chem.*, **1996**, 33, 7241.

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"Molecular Recognition and Reactivity of Ruthenium(II) Bipyridine Barbituric Acid Guest in the Presence of Noncovalently Bound Hosts: Ruthenium(II) Promoted Enolization of Barbituric Acids in Guest-Host Complexes" Chin, T.; Gao, Z.; Lelouche, I.; Shin, Y.-g. K.; Purandrai, A.; Knapp, S.; Isied, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 12849-12858.

"Ruthenium Tetraammine Chemistry of Self-assembled Monolayers on Gold Surfaces: Subsititution and Reactivity at the Monolayer Interface", Luo, J.; Isied, S. S. *Langmuir*, **1998**, 14, 3602-3606.

"Site-Dependent Stereoselective Binding of Ruthenium Aquobipyridine Complexes to Histidine Side Chains in Horse Heart Cytochrome c", Luo, J.; Wishart, J. F.; Isied, S. S. *J. Am. Chem. Soc.*, **1998**, 120, 12970-12971.

"Mechanistic Information from the First Volume for Intramolecular Electron-Transfer Reactions: Tetraammine-ruthenium(ligand) Complexes of Cytochrome c", Sun, J.; Su, C.; Meier, M.; Isied, S. S.; Wishart, J. F.; van Eldik. R *Inorg. Chem.* **1998**, 37, 6124-6135.

"Hydrogen bonding association of a ruthenium(II) bipyridine barbituric acid guest to complementary 2,6-diamino-pyridine amide hosts: guidelines for designing high binding hydrogen bonding cavities in both high- and low-polarity solvents", A. S. Salameh, A. S.; T. Ghaddar, T.; S. S. Isied, S. S. *J. Phys. Org. Chem.* **1999**, 12, 1-8.

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"Ruthenium Bisbipyridine Complexes of Horse Heart Cytochrome c: Characterization and Comparative Intramolecular Electron-Transfer Rates Determined by Pulse Radiolysis and Flash Photolysis", Luo, J. Reddy, K. B. Abdu S. Salameh, James F. Wishart, and Stephan S. Isied *Inorg Chem;* **2000**; 39(11); 2321-2329.

C. Manuscripts In Preparation

Z. Gao, Y-gyo K. Shin, J. F. Wishart, S. S. Isied, Long Range Electron Transfer Across Polypeptides: Interpretation of Rates in terms of Electron and Hole Superexchange and Hopping Mechanisms" manuscript in preparation.

Y-gyo K. Shin, M. D. Newton and S. S. Isied (**2000**) Energetics and Electronic Coupling Across Peptide Bridging Ligands: Effect of Protein Secondary Structure and the Direction Of Peptide Dipoles to be submitted to *J. Phys. Chem.*, manuscript in preparation.

T. .Ghaddar, S. S. Isied, "Metal Ion Binding to Collagen Peptides", manuscript in preparation.

J. Luo, T. Ghaddar, S. S. Isied, "Hydrogen-Bonding Promoted Electron Transfer in Ruthenium Osmium Guest-Host Complexes Immobilized on Self-assembled Monolayers", manuscript in preparation.

M. Y. Ogawa, A. Abrahim, I. Moreira, S. J. Milder, B. S. Brunschwig, J. F. Wishart, E. W. Castner, Jr.; S. S. Isied, "Photoinduced Intramolecular Electron Transfer across Oligoproline Peptides in $[(bpy)_2Ru^{II}L\text{-}(Pro)_n\text{-}Co^{III}(NH_3)_5]^{4+}$, n = 0-3" manuscript in preparation.

T. Chin, B. S. Brunschwig, Y-gyo. K. Shin, S. S. Isied, "Metal to Metal Intramolecular Electron Transfer across a class of Cross-linked α-Helical Hexapeptides: Analysis of Multi Electron Transfer Pathways" , manuscript in preparation.

R. Mobashar, S. S. Isied, "Oxidation Potentials of Peptides with Polarizable Amino Acid Side Chains and those Resulting from Polarizable Side Chain-Side Chain Interactions", manuscript in preparation

Talks And Invited Lectures Related to This Research (1996-2000)

Electron Transfer across Peptides with the Polyprolline II and Collagen Structures Gordon Conference on Photosynthesis, Kimball Union Academy, Meriden, NH., June 18-23, 2000, invited lecture.

Molecular Recognition and Electron Transfer across Hydrogen Bonding Networks , Univ. of Sao Paulo, San Carlos campus, San Carlos, Brazil, May 27, 2000, invited lecture.

Long Range Electron Transfer across Proteins and Peptides with the Polyproline II and Collagen Structures , 23 rd Meeting of the Brazilian Chemical Society, May 23-26, Pocos de Caldas, Brazil, invited lecture.

Mechanisms of Long Range Electron Transfer in Peptide Donor-Acceptor Complexes , Bioinorganic Meeting of NY Academy of Sciences, May 10, 2000, NY, invited lecture.

Molecular Recognition and Electron Transfer across Hydrogen Bonding Networks , 22nd DOE Solar Photochemistry Conference, Lake Tahoe, CA, June 7-11, 1999

Pulse Radiolysis Studies of Electron Transfer in Peptides and Proteins, Gordon Conference on Donor-Acceptor Complexes, Newport, R. I., August 7-12, 1998.

Electron Transfer in Peptides and Proteins: Models, Theory, and Experiments , Nov 1997, Rutgers Univ., Newark, NJ

Substitution and Electron Transfer Reactions of Ruthenium Ammines at Molecular Interfaces, Protein Surfaces and Monolayer Assemblies , Invited Talk, Gordon Conference on Radiation Chemistry,,Santa Barbara, CA., Mar 2-7, 1997.

Molecular Recognition and Charge Transfer across Hydrogen Bonding Networks , 21 st DOE Solar Photochemistry Conference, Copper Mt, CO, June 7-11, 1997

Chairman of Session on Electron Transfer in DNA , Gordon Conference on Donor-Acceptor Complexes, Newport, R. I., August 13-18, 1996.

Pulse Radiolysis Studies of Electron Transfer in Peptides and Proteins, Invited Talk, Gordon Conference on Radiation Chemistry , Newport, R. I., July 7-12, 1996.

Molecular Recognition and Charge Transfer across Hydrogen Bonding Networks , 20 th DOE Solar Photochemistry Conference, IN, June 8-12, 1996

Intramolecular Electron Transfer across Peptide Networks: Relationship to Electron Transfer in Proteins, Dept of Chemistry Colloquium, Univ. of Minnesota, Minneapolis, MN, April 18, 1996.

Metal to Metal Intramolecular Electron Transfer across Peptide Networks: Relationship to Electron Transfer in Proteins, Univ. of Iowa, Ames, IA, April 18, 1996.

"Substitution Reactions of Ruthenium and Osmium Tetraammine Complexes on Gold Electrodes modified with Alkyl Thiol Monomers" Panel on Solor Hydrogen Production, Conference on Research Opportunities in Photochemical Sciences, Estes Park, CO, Feb 5-8, 1996.

Metal to Metal Intramolecular Electron Transfer across Peptide Networks: Relationship to Electron Transfer in Proteins, SUNY, Stony Brook, NY, March 5, 1996.

Efficient Long Range Intramolecular Electron Transfer Pathways across Constrained, Helical Peptides, Univ. of Florida, Gainesville, FL, April 18, 1996.

D. Research Group

The PI research group at Rutgers consists of four graduate students, Allison Distefano (second year), Ruba Abdulmalek (second year), Tarek Ghaddar (fourth year), and Zhinong Gao (fifth year). Both second year students are working on DOE related projects. Two new undergraduate research students, Evita Sadimin and Leslie Chrzanowski, who have recently joined the group

are working peptide synthesis related to this project. Two new graduate students will be joining the group in September 2000.

The title of Mr. Ghaddar's Ph.D. Thesis is "Molecular Recognition and Electron Transfer Across Peptidomimetic and Peptide Interfaces". Mr. Ghaddar expects to complete his thesis work in the summer of 2000. Mr. Gao's thesis is "Through Space and Through Bond Electron Transfer in Transition Metal Donor-Acceptor Mixed Oligoproline Peptides". Mr. Gao expects to complete his thesis work in 2000. Dr. J. Luo currently holds a Research Associate Position in the group and Dr. Y. Shin is also a part-time Research Associate / Faculty.

E. Facilities

The Department of Chemistry at Rutgers University maintains a number of Departmental facilities which the PI and his group have access to. The Departmental facilities include an *x-ray crystallography lab* with low temperature capability equipment run by a university staff scientist (Dr. Tom Emge) and *High field NMR instrumentation* (200, 400, 500, and 600 MHz) with multinuclear and solid state NMR capabilities also run by a staff scientist. These facilities also include *high level Electronics Staff* capable of designing electronic circuits for the interface of electronic equipment with computers. *Multiuser computational facilities* with high performance computers and a trained staff for assisting graduate students and faculty in the use of different software packages for molecular modeling and electronic structure calculations are available. A *spectroscopy lab* with several CD, IR, and Raman instruments is also housed in the Chemistry Department. A mass spectrometry facility is located at Cook College (5 miles from the Chemistry Dept).

The PI has a well equipped laboratory of ~2,000 sq ft. The lab is well equipped for the synthesis of peptides and transition metal complexes with several high pressure liquid chromatographs (HPLC) including one with with a diode array detection system. Electrochemical equipment (BAS 100 and EG&G), a PARC 273 Potentiostat and a PARC 175 universal programmer, and a fast techtronix scope are also available. An HP diode array UV-Vis spectrometer, a Spex Fluoromax fluorometer and stopped flow

instrumentation are also available. The PI has computing and modeling capabilities with a CAChe Worksystem v. 3.8, (Beaverton, OR) on a Macintosh 8500.

The PI has a Laser Flash Photolysis apparatus for determination of lifetimes in the nanosecond timescale, as well as, transient absorption measurements in the visible region. This equipment (assembled from a new grant from Rutgers University ($40,000) as a match to the previous DOE funded grants) is now totally dedicated to this DOE project. Collaborative arrangements for picosecond and femtosecond lifetime measurements have been arranged with Prof. Ed Castner who has just joined our Department from Brookhaven National Laboratories.

Collaborative arrangements with the Brookhaven National Laboratory for pulse radiolysis and laser flash photolysis work are well established. The PI has a continuing adjunct appointment at Brookhaven National Laboratory, where he has had very successful collaboration with Dr. James Wishart of the Radiation Chemistry Group and Dr.Bruce Brunschwig of the Photochemistry group, and more recently with Dr. Marshall Newton (see letter). These collaborative arrangements with Brookhaven National Lab constitute an essential part of this proposal.